Title

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Journal

Journal of perinatology : official journal of the California Perinatal Association, 39(1)

ISSN

0743-8346

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Publication Date

2019

DOI

10.1038/s41372-018-0258-9

Peer reviewed

Published in final edited form as:

J Perinatol. 2019 January ; 39(1): 86–94. doi:10.1038/s41372-018-0258-9.

Factors Influencing Decision-Making in Neonatology: Inhaled Nitric Oxide in Preterm Infants

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Abstract

Objective: We studied decision-making regarding inhaled nitric oxide (iNO) in preterm infants with Pulmonary Hypertension (PH).

Study Design: We asked members of the AAP-Society of Neonatal-Perinatal Medicine and Division-Chiefs to select from three management options-initiate iNO, engage parents in shared-decision-making or not consider iNO in an extremely preterm with PH followed by rating of factors influencing their decision.

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Contributor's statement page

Drs. Manja, Jack, Monteiro and Lakshminrusimha conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Drs. Guyatt and You conceptualized the study, supervised data collection, and critically reviewed the manuscript for important intellectual content.

Drs. Kirpalani, Zupancic and Dukhovny conceptualized the study, reviewed and analyzed data, and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Financial disclosure: All authors have indicated that they do not have any financial relationships relevant to this article to disclose.

Conflicts of interest: All authors have indicated that they have no potential conflicts of interest to disclose.

Conflict of interest: The authors have no competing financial interests in relation to the work described.

Results: 304 respondents (9%) completed the survey; 36.5% chose to initiate iNO, 42% to engage parents, and 21.5% did not consider iNO. Provider's prior experience, safety, and patient-centered care were rated higher by those who initiated or offered iNO; lack of effectiveness and cost-considerations by participants who did not chose iNO.

Conclusions: Most neonatologists offer or initiate iNO therapy based on their individual experience. The minority who chose not to consider iNO placed higher value on lack of effectiveness and cost. These results demonstrate a tension between evidence and pathophysiology-based-therapy/personal experience.

Keywords

hypoxic respiratory failure; prematurity; cost-effectiveness; evidence based medicine; medical decision making; clinical practice guidelines

Pulmonary hypertension (PH) affects 8.1% of extremely preterm neonates and is associated with high mortality (20.5%) and morbidity.[1] Treatment options are limited and include inhaled nitric oxide (iNO) and sildenafil. These therapies are not approved in preterm infants by the US Food and Drug Administration. Although iNO is a proven effective[2] treatment strategy in term and near-term infants with persistent PH of the newborn, its efficacy in preterm neonates is less certain.[3] An individual patient level meta-analysis of premature infants enrolled in randomized controlled trials using iNO found no significant effect on death or chronic lung disease [4]; a Cochrane review found no improvement in outcomes with iNO with a potential for harm in the form of severe intraventricular hemorrhage.[5] Selective use of iNO among preterm infants with hypoxemic respiratory failure (HRF) associated with oligohydramnios and pulmonary hypoplasia [6,7,8] and/or echocardiographic evidence of PH [9, 10] is considered by several experts in the field and is an option according to The National Institute of Health (NIH) [11] and American Heart Association/American Thoracic Society (AHA/ATS) guideline[12] recommendations. However, the American Academy of Pediatrics' (AAP) Committee of the Fetus and Newborn [3] clinical report makes no such exception based on randomized controlled trials evaluating preterm infants with respiratory failure. It states that neither rescue nor routine use of iNO improves survival in preterm infants with respiratory failure. This decision was based on studies, which did not have treatment of specific PH as their primary objective. The NIH consensus statement (2011),[11] AAP (2014), [3] AHA/ATS (2015),[12] and Pediatric Pulmonary Hypertension Society guidelines (2016) [14] and the Cochrane review results are summarized in Table 1. Selective use of iNO in infants with pulmonary hypoplasia and PH, as documented by echocardiography, (this is recommended by the Pediatric Pulmonary Hypertension Society guidelines[14]) has not been evaluated in a large randomized, controlled trial. Therapy with iNO is expensive (average approximately $125 [15] to $147 USD per hour of use irrespective of dose), cost varies based on contractual agreements.

Despite limited evidence for benefit and the potential for harm, the use of iNO in preterm infants with PH and/or HRF is common.[16] The use of iNO among preterm infants has not decreased after publication of the AAP clinical practice guidelines (CPGs). Finer and Evans opine that this persistent use of iNO in preterm infants is not due to ignorance of the evidence; rather an instinct to attempt to normalize physiology of PH when faced with a

hypoxemic infant.[17] There is a paucity of randomized controlled trials evaluating the effect of iNO on mortality in extremely preterm infants with pretreatment echocardiographic evidence of PH. [1813] Understanding the factors that influence use of iNO in preterm infants is essential to designing and implementing strategies that will increase evidence-based high-value care.

Therefore, using a clinical vignette of an extremely premature infant with PH and HRF associated with prolonged rupture of membranes, we asked neonatologists to specify the importance of factors in deciding whether to use iNO. The purpose of this study was to address determinants of neonatologists' clinical decisions in the setting of limited evidence of effectiveness, high resource use, and conflicting CPG recommendations. We also evaluated reasons for failure to implement the evidence and value based AAP clinical report.

Materials and Methods

The study was approved by the Institutional review board at the University at Buffalo, Buffalo New York, USA and the Hamilton Integrated Research Ethics Board at McMaster University, Hamilton, Ontario, Canada. The details of the study protocol for conducting surveys using clinical vignettes and analysis of data to determine factors influencing clinical-decision making were published in the European Journal of Person Centered Healthcare [19].

To capture the elements of quality of healthcare, many organizations [20] and researchers[21] have adopted the Institute of Medicine (IOM)'s framework for quality of care [22]. This framework organizes the determinants of quality into six domains: safety, effectiveness (evidence-based), patient-centered-care, timely, efficient (cost considerations) and equitable. The domains of timeliness and equity were not applicable to the clinical vignette presented in this study, the remaining four domains and three additional factors that may influence clinical decisions including local hospital practice[23, 24], medicolegal concerns[25] and provider's prior experience[26] were included in this study.

Development of the survey:

Experienced clinicians and researchers in neonatology developed the case description. The clinical sensibility of the case scenario was confirmed during pilot testing with a group of 12 neonatologists and the survey was modified based on their feedback. A second round of pilot testing was performed with a separate group of five neonatologists and confirmed the clinical sensibility of the case scenario, response options and the factors included for rating.

Case description

Figure 1 presents the final case description. This was designed such that the infant *would* meet criteria for initiation of iNO therapy based on the PH physiology-based-approach as per the ATS/AHA guidelines [12], include an option for possible shared decision-making (SDM) according to NIH guidelines but *would not* meet the AAP clinical report guidelines [3] for treatment. Respondents chose from three responses regarding the use of iNO: Initiate iNO; explicitly discuss the potential benefits, side effects and costs with parents before making a decision to offer iNO (SDM); or not to consider iNO. After choosing one of the

three options, participants rated the importance of the seven factors in their decision on a 7-point Likert scale from ‘unimportant’ to ‘critically important’. Participants then reviewed current CPG recommendations, were asked to reflect further on their decision, and asked whether the additional information changed their management plan (yes or no response). Respondents had the opportunity to provide a free text response commenting on their reasoning. Finally, respondents reviewed a scenario of payment refusal by the third-party payer resulting in financial burden to parents followed by a question asking if this additional information would change their clinical decision (yes or no response) and an opportunity to provide comments.

Survey administration:

The survey was anonymous, administered via email through the Section on Neonatal Perinatal Medicine (SoNPM) of the AAP (approximately 3302 email addresses at the time of this survey) [27] on September 29, 2017 and to Neonatology Division Chiefs email list (113 members on the day of the survey) on November 10, 2017 using a URL (uniform resource locator) link. The mailing list of SoNPM includes 100 neonatal nurse practitioners, 350 fellows and 200 Pediatricians. Many members of the Neonatal Division chiefs mailing list are also members of the SoNPM. The survey was conducted and data collected using the SurveyMonkey® platform (SurveyMonkey®, San Mateo CA).

Statistical Analysis:

Results were analyzed in IBM SPSS statistics for windows (IBM, Armonk NY). All data were explored using descriptive statistics. To determine if the average ratings of the seven factors differed relative to the management option selected, we conducted a repeated measures analysis of variance (ANOVA). The ratings of the seven factors were included as within subject factors and the choice of management option as a between subjects factor. Further exploration of possible interactions was conducted using a multinomial logistic regression. The dependent variable had three management options as the outcomes (initiate iNO, SDM or not consider iNO). The independent variables were the seven factors. The reference category for this analysis was the option to not offer iNO therapy. The association of demographic characteristics with selection of management plan was examined using chi-squared tests. Free text responses were analyzed using basic content analytic strategies.[28, 29]

Results

Of 336 participants who started the survey, 90% completed it. Majority of respondents (61%) were from an academic setting, 24% from private practice, 12% were hospital employees and 3% had other affiliations. Almost half (45%) of respondents had > 20 years in practice, 24% had practiced for 10-20 years and 31% had practiced for less than 10 years. The gender distribution was similar (52% male; 48% female).

The most frequent option selected (42%) was offering iNO therapy after shared decision with parents. More than a third (36.5%) chose to initiate iNO treatment; a minority (21.5%) chose not to consider iNO (figure 2). Based on the results of chi-square tests, there was no

influence of practice setting, years in practice, or gender of the treating neonatologist on treatment choice.

In the repeated measures ANOVA, ratings of the importance of the factors differed ($F(6, 1644) = 104.58$, $p < 0.001$). Of the seven factors rated, overall among all participants, safety, effectiveness (evidence-based care) and provider's prior experience were rated highest. Cost considerations, local hospital practice and medicolegal concerns were rated as least important. Table 2 summarizes the odds ratio for ratings for these factors. The rating of the seven factors differed based on the management option selected with a significant interaction ($F(12, 1644) = 9.7$, $p < 0.001$); this interaction was described using multinomial logistics regression (Table 2). Evidence on the lack of effectiveness and cost considerations were rated highest by physicians who did not consider iNO therapy. Patient-centered-care was rated highest by physicians who opted for SDM and provider's prior experience and safety were rated highest by physicians who chose to initiate iNO therapy (figure 2).

Forty-five percent of neonatologists who chose to initiate iNO therapy and 49% who chose SDM indicated that the additional information from CPG would influence their decision; 18% physicians (4% of all surveyed providers) who had chosen not to use this treatment noted that additional information on CPG would influence their decision(figure 2). Adding information on costs, and an anecdotal instance of a parent being liable for treatment costs led to a third (35%) of participants responding that this would influence their decision-making but was not significantly different between the three initial management strategy groups.

Participants provided extensive comments to the free text options, contributing 148 comments in response to the first follow-up question with CPG recommendations and 192 comments in response to the cost and potential out-of-pocket costs to parents. The major concepts that were communicated along with explanations and select quotes are presented in Supplemental tables 1 and 2.

Analysis of comments reveals that most clinicians are aware of the limited evidence and the controversy surrounding its use in preterm infants including cost concerns. However, when making individual patient care decisions, other factors including absence of alternative treatment and the expectation by parents to 'do something/do everything' become compelling reasons to use iNO; much emphasis was on the clinician's prior anecdotal experience of success in improving oxygenation in a similar infant.

In response to a hypothetical scenario of insurance denial resulting in significant out-of-pocket expenses for the parent, almost a third of respondents suggested they would treat despite the costs; some stating that they do not consider costs when treating patients, or that costs should not be considered. 27% of respondents stated that they would discuss the cost issue with parents, however how the discussion would impact decision making was not clear. 13% of respondents suggested that their hospital or health system would absorb costs and the patient would not have individual liability.

Discussion

This study addresses policy implementation and clinical decision making regarding the use of a therapy based on pathophysiology for a critically ill premature infant with PH and HRF in the face of limited evidence of benefit, potential for harm and high cost using the example of iNO. To our knowledge, this is the first study addressing factors influencing provider decision-making in neonatal medicine.

Despite recommendations from AAP against the use of iNO, most respondents chose to initiate or offer this therapy. The minority who chose not to consider iNO based their decision on the lack of supporting evidence and cost concerns; however, 18% in this group indicated that the AHA/ATS CPG recommendations basing therapy on pathophysiology would influence their decision (figure 2).

Review of comments suggests that most neonatologists who initiate or offer iNO are aware of the current trial evidence and cost concerns, however, other factors including safety and patient centered care play a dominant role during their decision making leading them to choose options that are not effective and expensive. A recent study corroborates our findings, reporting that although clinicians understand and appreciate the concept of limiting unnecessary testing and treatment, they find it difficult to implement this in practice, partly due to their prior experience and the perception of patient expectations [30]. In our study, prior experience was rated as an important consideration by the group choosing iNO therapy; providers believe, in part based on their own experience, that failure to show a benefit in a group of patients in the setting of a randomized control trial does not exclude the possibility that the treatment will benefit a specific individual infant. A desire to try all options irrespective of costs, pressure from parents to do everything possible, community standards and expectations and medicolegal concerns represent other reasons clinicians chose to treat or offer iNO.

These findings are consistent with those of other studies. It is well known that short-term improvement in oxygenation is observed among term and preterm infants with HRF [31] and when facing the ‘gravest of circumstances’, neonatologists initiate iNO therapy in an act of ‘hopeful desperation – it is better to try something than do nothing’. [32] From a physiological perspective, after optimization of ventilation and hemodynamics and in the presence of echocardiographic evidence of PH, therapy with iNO can potentially improve pulmonary blood flow and improve oxygenation. [33]

The selective use of iNO for preterm infants with PH physiology and HRF associated with PROM with possible pulmonary hypoplasia (physiology-based approach) warrants further discussion. Recruitment of preterm infants only with confirmed PH, hypoplasia and HRF in trials will prove challenging, but are needed. However, data from subsets of patients in RCTs and observational data suggest a benefit. Desandes et al randomized 70 preterm infants with HRF and observed improvement in oxygenation only among the subset of 28 infants with low pulmonary blood flow by echocardiography (11/35 with iNO and 17/35 controls). [34] Chock et al evaluated 12 patients with PROM, oligohydramnios and pulmonary hypoplasia among the 449 infants enrolled in the Neonatal Research Network PiNO trial. A trend

towards improved oxygenation (39±50 mmHg increase vs.a decrease of 11±15) and lower mortality (33% vs. 67%), BPD (40% vs.100%) and severe IVH/PVL (1/5 vs.1/2 subjects) is suggested in the iNO group compared to controls. [7] In a retrospective audit of infants in Australia and New Zealand, functional echocardiography identified preterm infants with PH earlier and at a lower OI, but it did not improve survival to discharge. [35] Single-center studies also demonstrate survival benefit with iNO among preterm infants with HRF and PPROM. [8] Finally, the large, retrospective study from the Pediatrix Database showed a trend towards lower mortality among preterm infants with pulmonary hypoplasia and PH (Hazard Ratio – 0.67; 95% confidence interval – 0.45-1.01). [6]

In contrast, the trials that led to the AAP Committee of Fetus and Newborn report and Cochrane report were randomized trials predominantly based on HRF in preterm infants without any evidence of long-term benefit. Based on comments written by the survey respondents (Supplemental table 1), many practicing neonatal providers are either not confident about the results of the randomized trials – or are confused about conflicting summaries. The guidelines written by respected physician-scientists and published by ATS/AHA and Pediatric Pulmonary Hypertension Network[12, 14] and based on pathophysiology is appealing to many practicing providers. Personal anecdotal experience of improved oxygenation following initiation of iNO led to the use of best clinical judgement when caring for each individual infant even if it contradicted NIH/AAP recommendations. Lack of alternative therapies and pressure from patients and staff were also cited as reasons to initiate iNO. (figure 2) Alternative therapies used for the treatment of PH in preterm infants such as sildenafil [36] have a physiological rationale and variable effectiveness based on small studies, However, chronic oral sildenafil is the mainstay of long-term PH therapy and continues to be used in clinical practice. [37] They are relatively inexpensive compared to iNO and as a result have elicited less controversy.

A Cochrane review on this topic [2] concluded that early routine use of iNO in preterm infants with HRF does not prevent serious brain injury or improve survival. This review also reported a statistically not significant 20% increase in brain injury with iNO (RR 1.2; 95% confidence interval .98 – 1.47). In this review, the quality of evidence was judged as moderate to high using the GRADE framework [38]. More recently, an epidemiological study has linked iNO use with a small increase in childhood cancer. [39] Interestingly, the potential for harm was not considered in any of the comments. We speculate that neonatologists feel that iNO therapy is safe in preterm infants and the increase in brain injury was observed in one study [40] but not in other trials. [41, 42]

Our study has several strengths including a very specific case-based scenario exploring the factors that influenced decisions. This design provided a measurement of the relative influence of various factors in clinical decision making by clinicians in diverse practice settings. We had a robust response to our invitation for free-text responses with over half of respondents providing comments and explanations leading to a richer understanding of the decision-making process. This study confirms the opinions of Finer and Evans [17] and Soll [18] regarding reasons for continued use of iNO among preterm infants by neonatal practitioners.

This study has several limitations. The case description was brief and did not include information regarding ductal and atrial level shunting. Providing this information could have enabled respondents to accurately diagnose the presence of PH. The case-based surveys are time and effort intensive, and our response rate was low. Our response rate is typical of many current surveys, reflecting the decline in response rates of both the general public (from 21% in 2006 to 9% in 2016) [43] and physicians who have response rates even lower than the general public. [44] This is also true of surveys sent to members of AAP SONPM (between 250-300 responses - personal communication with Mr. James Couto, AAP). The potential respondent bias associated with the low response raises the possibility that the results may not be representative of practicing neonatologists in the US.

Currently there is an increasing focus on considering costs and cost effectiveness [45, 46] in medical decision-making. Designing strategies to provide 'high-value' care is of tremendous interest and much has been written on this topic by professional societies. [47] Current policy initiative such as the Choosing Wisely®[48] campaign target education and knowledge translation strategies to increase appropriate use of medical technologies but do not consider factors that may influence physician's judgement during decision making; these efforts have resulted in minimal impact[49] or even a contrarian effect[50]. Successfully designing and implementing strategies to increase 'high-value' care have proved challenging [51]. Although a significant proportion of neonatologists indicated that review of CPG would influence their decision, many chose to consider iNO treatment in spite of the knowledge of the evidence and guidelines and the majority did not change their decision based on the review of CPG recommendations. Factors other than knowledge of the evidence and CPG recommendations play a decisive role in decision-making. The results of this study suggest that current education and knowledge translation strategies while important are not sufficient and an improved understanding and targeting of the factors that motivate physician's decisions is essential in designing successful implementation strategies. These may include improved efforts to support physicians and parents during difficult decision-making process, especially in critical care and increased parent and community engagement.

Conclusions

Most neonatologists chose to offer or initiate iNO treatment based on their previous experience and the need to provide patient centered care perceived as a necessity to try all options in a critically ill extremely premature infant. The results demonstrate a tension between a physiology-based approach backed by anecdotal personal clinical experience and an approach based on evidence of effectiveness in clinical trials that needs to be addressed to successfully implement high-value care. One approach to resolve this tension is to gather more data in preterm infants with PH and HRF. Due to lack of equipoise and difficulties with funding and recruitment, placebo controlled trials are unlikely in this population. Alternative study designs such as prospective multicenter registries (one such registry is being organized by Dr. Kinsella-personal communication), and adaptive designs may be helpful in addressing issues regarding the efficacy and safety of therapeutic options in extremely preterm infants with life threatening hypoxemia due to PH physiology. The second approach would be to develop guideline implementation strategies that include efforts beyond traditional clinician education. "Academic detailing" to prospectively collect

prescribing patterns of individual physicians and short- and long-term outcomes of patients followed by an interactive discussion of bias and data deficits may be an effective strategy.[52] Further research into the psychology of clinical decision-making is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

NICHD for grant support (SL)

Funding source: NIH 2 R01 HD072929 06 (SL),

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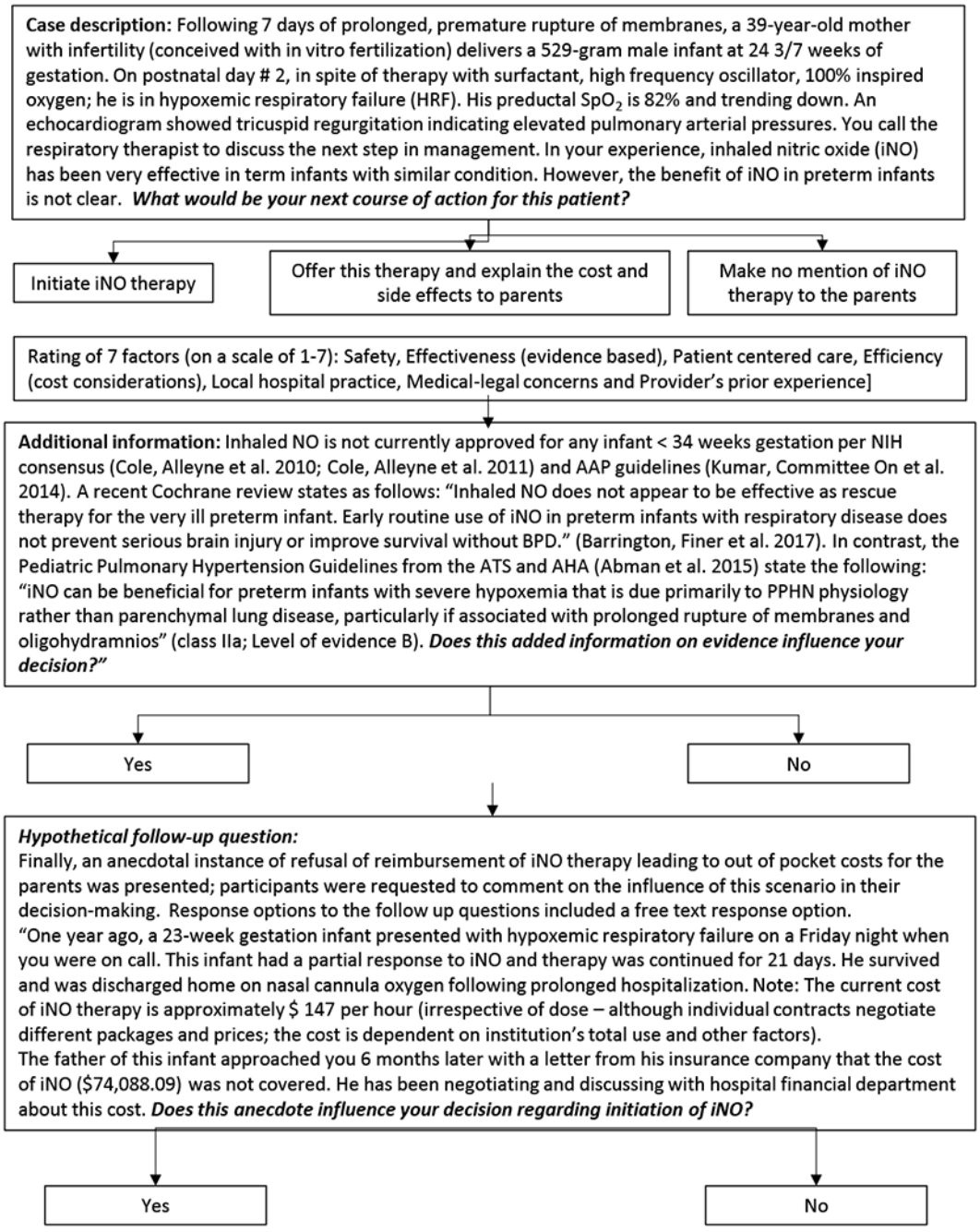

Figure 1.
Clinical vignette used for the survey. Free text responses were obtained following each follow-up question.

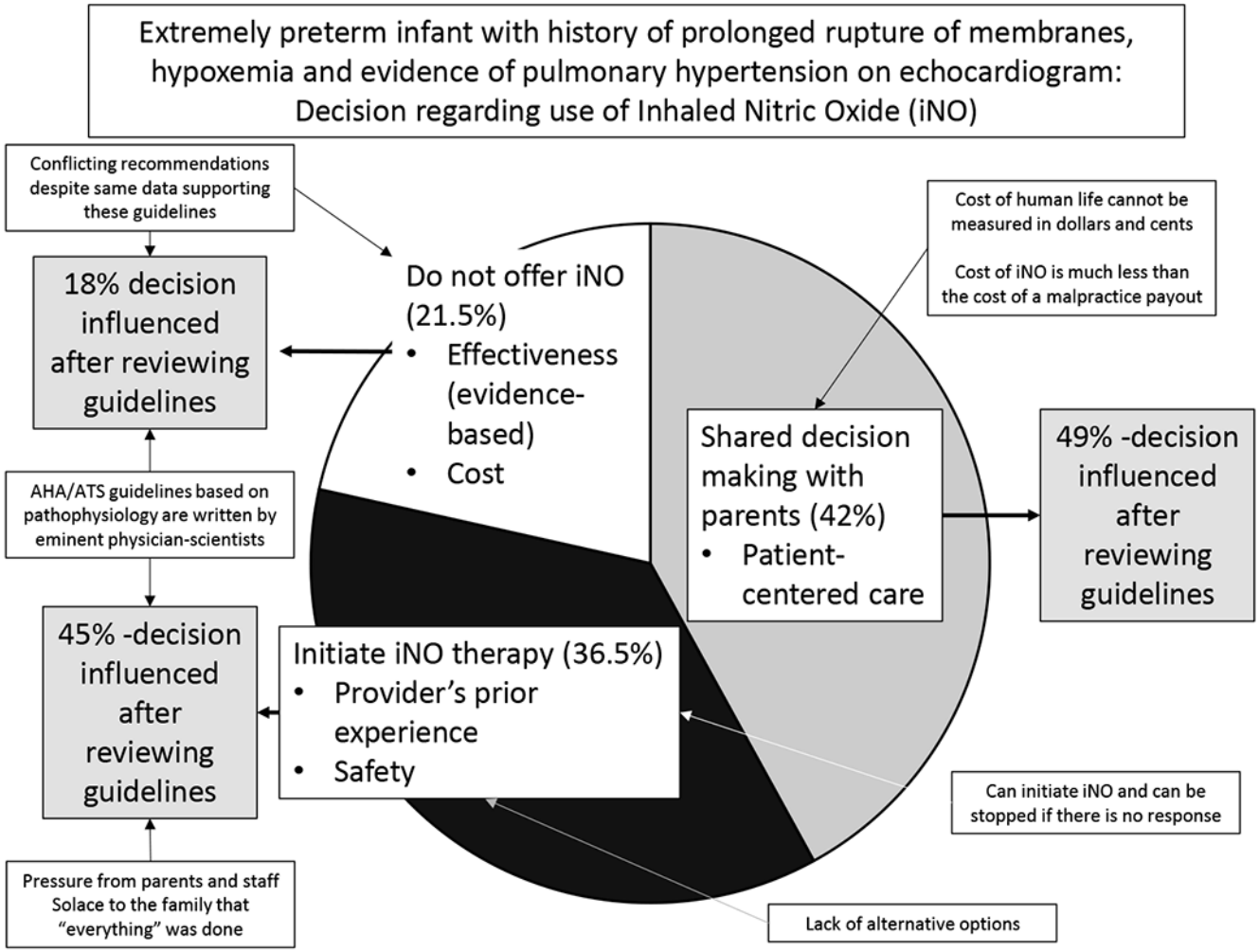

Figure 2.

Pie chart demonstrating decision regarding initiation of therapy with inhaled nitric oxide and the main factors influencing this decision (bullet points). The percentage of respondents whose decision was influenced by reviewing current practice guidelines in table 1 are shown in boxes outside the pie chart. Some pertinent comments provided by respondents are shown in small font.

Table 1.

Summary of clinical practice guidelines – use of iNO in preterms for pulmonary hypertension or hypoxemic respiratory failure

Source (year)	Recommendations
NIH consensus (2011)[9]	• Taken as a whole, the available evidence does not support use of iNO in early-routine, early-rescue, or later rescue regimens in the care of premature infants of 34 weeks' gestation who require respiratory support. • There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which iNO may have benefit in infants of < 34 weeks' gestation. In such situations, clinicians should communicate with families regarding the current evidence on its risks and benefits as well as remaining uncertainties.
AAP 2014[3]	• The results of randomized controlled trials, traditional meta-analyses, and an individualized patient data meta-analysis study indicate that neither rescue nor routine use of iNO improves survival in preterm infants with respiratory failure *(Evidence quality, A; Grade of recommendation, strong)*. • The preponderance of evidence does not support treating preterm infants who have respiratory failure with iNO for the purpose of preventing/ ameliorating BPD, severe intraventricular hemorrhage, or other neonatal morbidities (*Evidence quality, A; Grade of recommendation, strong*). • The incidence of cerebral palsy, neurodevelopmental impairment, or cognitive impairment in preterm infants treated with iNO is similar to that of control infants (*Evidence quality, A*).
AHA/ATS 2015[10]	• iNO can be beneficial for preterm infants with severe hypoxemia that is due primarily to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios (*Class IIa; Level of Evidence B*).
Pediatric Pulmonary Hypertension Network 2016[11]	• iNO therapy can be beneficial for preterm infants with severe hypoxemia that is primarily due to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios; • 2. iNO is preferred over other pulmonary vasodilators in preterm infants based on a strong safety signal from short- and long-term follow-up of large numbers of patients from multicenter randomized clinical trials for BPD prevention.
Cochrane review 2017[2]	• This review suggests that no clear indications are known for inhaled nitric oxide (iNO) in preterm infants. • Early rescue treatment does not appear successful and may lead to a non-significant increase in brain injury. However, preterm infants with clear evidence of pulmonary hypertension have not been separately identified in these studies and may constitute a subgroup with a different response.

Table 2.

The importance of factors influencing clinical decisions to initiate, discuss and offer or not consider iNO therapy in extremely preterm infants with pulmonary hypertension and hypoxemic respiratory failure. The reference category is – 'make no mention of iNO therapy to parents'

Factor	Option	OR (95%CI)	Significance
Safety	Initiate iNO	1.49 (1.1-2.0)	0.009
	Shared decision making with parents	1.38 (1.05-1.83)	0.023
Effectiveness (evidence-based)	Initiate iNO	0.39 (0.27-0.58)	<0.0001
	Shared decision making with parents	0.53 (0.37-0.77)	0.001
Patient centered	Initiate iNO	1.39 (1.1-1.75)	0.006
	Shared decision making with parents	1.7 (1.35-2.13)	<0.0001
Efficient (Cost)	Initiate iNO	0.76 (0.59-0.99)	0.038
	Shared decision making with parents	0.79 (0.62-1.0)	0.045
Local practice	Initiate iNO	1.06 (0.81-1.37)	0.687
	Shared decision making with parents	1.06 (0.83-1.36)	0.665
Medicolegal concerns	Initiate iNO	1.0 (0.79-1.26)	0.993
	Shared decision making with parents	1.15 (0.93-1.44)	0.203
Prior experience	Initiate iNO	1.81 (1.32-2.49)	<0.0001
	Shared decision making with parents	1.05 (0.79-1.39)	0.733

Interpretation of the odds ratio (OR) – The odds of choosing a given option (either to initiate iNO or to offer iNO after shared decision-making) over the reference option (not consider iNO) for every unit increase in the independent variable (importance rating on the 7-point Likert scale from 1=unimportant to 7=critically important). For example, interpretation of the OR for safety in the initiate iNO group - As the rating for safety increases by one unit, the odds of choosing the option to initiate iNO increases by 49% (OR 1.49). For OR of <1, the odds decrease – for example interpretation of the OR for effective – as the rating for effective increase by 1 unit, the odds of choosing to initiate iNO decrease by 61% (1 - 0.39).